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S rial No. 10/071,247

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: Gary Griffiths

Title: FLUORINATION OF PROTEINS AND
PEPTIDES FOR F-18 POSITRON
EMISSION TOMOGRAPHY

Appl. No.: 10/071,247

Filing Date: 02/11/2002

Examiner: Huynh, P.

Art Unit: 1644

BRIEF ON APPEAL

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BOARD OF PATENT APPEALS AND INTERFERENCES

Attorney Docket No. 018733/1093

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APPELLANT'S BRIEF UNDER 37 CFR §1.192

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

This brief is in furtherance of the Notice of Appeal filed in this case on September 11, 2003. The fees required under 37 CFR §1.17(f) are included in the attached check. Please charge any fee deficiency or credit any overpayment to Deposit Account 19-0741.

This brief is transmitted in triplicate in conformance with 37 CFR §1.192(a).

I. REAL PARTY IN INTEREST

The real party in interest in this case is Immunomedics, Inc., as evidenced by an assignment recorded on February 4, 1999 at Reel/Frame 9759/0057.

II. RELATED APPEALS AND INTERFERENCES

Appellant, appellant's legal representatives, and the assignee are aware of no appeal or interference which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Canceled: 1-8

Pending: 9-20

Objected: 13-15

Rejected: 9-12 and 16-20

Appealed: 9-12 and 16-20

IV. STATUS OF AMENDMENTS

All claim amendments have been entered into the record, and appellant's arguments after Final Rejection have been considered, as indicated in an Advisory Action dated September 8, 2003.

V. BACKGROUND AND SUMMARY OF THE INVENTION

Positron emission tomography (PET) is a high resolution, non-invasive, imaging technique for the visualization of human disease. In PET, 511 keV gamma photons produced during positron annihilation decay are detected. In the clinical setting, fluorine-18 (F-18) is one of the most widely used positron-emitting nuclides. F-18 has a half-life ($t_{1/2}$) of 110 minutes, and emits β^+ particles at an energy of 635 keV. It is 97% abundant.¹

¹ Specification at page 1, lines 13-18.

The short half-life of F-18 has limited or precluded its use with longer-lived specific targeting vectors such as antibodies, antibody fragments, recombinant antibody constructs and longer-lived receptor-targeted peptides. In addition, complicated chemistry has been required to link the inorganic fluoride species to such organic targeting vectors. In typical synthesis methods, an intermediate is radiofluorinated, and the F-18-labeled intermediate is purified for coupling to protein amino groups. See, e.g., Lang *et al.*, *Appl. Radiat. Isol.*, 45 (12): 1155-63 (1994); Vaidyanathan *et al.*, *Bioconj. Chem.*, 5: 352-56 (1994).²

These methods are tedious to perform and require the efforts of specialized professional chemists. They are not amenable to kit formulations for use in a clinical setting. Multiple purifications of intermediates are commonly required, and the final step, involving linkage to protein lysine residues, usually results in 30-60 % yields, necessitating a further purification step prior to patient administration. In addition, these methods result in fluorinated targeting species which accumulate in the kidney, somewhat like radiometals.³

It was recently reported that ¹⁸F-fluoriodomethane (¹⁸FCH₂I) is a useful intermediate for the fluorination of organic intermediates. Zheng *et al.*, *J. Nucl. Med.*, 38: 177P (Abs. 761) (1997). In this process, diiodomethane is fluorinated with the F-18 ion by a room temperature reaction in acetonitrile solvent, resulting in up to a 40% yield. The ¹⁸FCH₂I is then distilled into reaction vials containing various strong nucleophiles in anhydrous acetonitrile and allowed to react at 80°C for fifteen minutes. Nucleophilic attack by carboxylates, thiolates, phenolates, and amines in particular, replaces the remaining iodine of ¹⁸FCH₂I, with overall yields of 10 to 35 %. The reaction products can be purified by reverse-phase HPLC. Fluoromethyl

² Specification at page 1, lines 19-26.

³ Specification at page 2, lines 1-7.

diethylamine, fluoromethyl benzoate, fluoromethyl benzyl thioether and fluoromethyl 4-(2-hydroxy-3-aminopropoxy)-carbazole have been made by this method.⁴

As discussed above, the currently available methods for labeling protein-based targeting vectors with F-18 are unsuitable. There is a need, therefore, for a simple, efficient method for incorporating the F-18 radionuclide into peptide-containing targeting vectors, such as proteins, antibodies, antibody fragments, and receptor-targeted peptides, to allow the use of such targeting vectors in routine clinical positron emission tomography.⁵

The present invention teaches methods for radiolabeling proteins and peptides with fluorine-18 (F-18). More particularly, these proteins and peptides are radiolabeled with F-18 by reacting a thiol group contained therein with an F-18-bound labeling reagent which also has a group that is reactive with thiols. The resulting F-18-labeled proteins and peptides are useful in imaging targeted tissue by clinical positron emission tomography.⁶

More particularly, the claims on appeal are directed to methods for detecting a tissue, comprising:

(a) administering to a patient a bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to an F-18-labeled peptide or a low molecular weight hapten conjugated to the F-18-labeled peptide; and allowing the bispecific antibody or antibody fragment to bind to the target tissue, and the non-targeted bispecific antibody or antibody fragment to clear;

⁴ Specification at page 2, lines 8-18.

⁵ Specification at page 2, lines 19-24.

⁶ Specification at page 1, lines 6-11.

(b) administering the F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing the F-18-labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear; and

(c) detecting the F-18-labeled peptide, thereby detecting the target tissue.⁷

VI. ISSUES

There are two issues in the present case, both stated under the first paragraph of Section 112.

The first issue is whether the specification enables a skilled artisan to practice the invention as recited in claims 9-12 and 16-20.

The second issue is whether the specification reasonably provides a written description of the invention, such that those skilled in the relevant art are apprised that the inventor, at the time the application was filed, had possession of the invention claimed in claims -12 and 16-20.

VII. GROUPS OF CLAIMS

For purposes of the present appeal, the claims do not all stand or fall together, but will be argued separately according to the following groups:

Group 1 Claims 9 and 16-20

Group 2 Claim 11

Group 3 Claims 10 and 12

⁷ See claim 9.

Arguments supporting patentability of Group 1 are found in Section IX.A. and IX.B. of the Brief. Arguments demonstrating additional bases for patentability of Groups 2 and 3, respectively, are presented in Section IX.C. of the Brief.

VIII. SUMMARY OF THE ARGUMENT

In general, the rejections appear to be based on a misunderstanding. The presently claimed invention is utilized in a wide range of known bi-specific antibodies and provides the chemistry to successfully label F-18 onto a wide variety of peptides for use in these known methods. The rejections improperly focus on the unpredictability of amino acid sequences rather than on the question of whether one of ordinary skill could successfully apply the labeling technique to diverse amino acid sequences. As to this latter issue, nothing in the rejections suggests only such difficulties. The specification enables the detection of tissue using bispecific antibodies and fragments having one arm specific to F-18 labeled peptides other than those specifically recited in claims 13-15. Although the examiner alleges that the specification only is enabling for a method for detecting a tissue in a patient by administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to one of the specific F-18 labeled peptides that are recited in claims 13-15, or a low molecular weight hapten conjugated to one of these F-18 labeled peptides, and then administering one of the specific F-18 labeled peptides recited in claims 13-15 or the hapten conjugate thereof, and detecting that F-18 labeled peptide by positron emission tomography, the record indicates that a skilled artisan is able to practice the invention across the full scope of claim 9. Neither the fact that the structure of an F-18 labeled peptide is not specified, nor the fact that different peptide sequences produce antibodies that have different specificities, leads to a conclusion of lack of enablement for bispecific antibodies and fragments that are specific to an F-18 labeled peptide. Similarly, bispecific

antibodies and fragments that have "an arm that is specific to a target tissue of the patient" also are fully enabled.

The other bases for lack of enablement are similarly unfounded. No additional reasons in support of five of six listed embodiments is provided. With respect to the last, the examiner argues that there are no *in vivo* working examples demonstrating that any antibody with unknown specificity would be useful in a method of detecting a tissue in a patient using PET. However, in the clinical setting, fluorine-18 (F-18) is one of the most widely used positron-emitting nuclides, and a skilled clinician would be fully enabled to practice PET with the F-18 labeled peptides according to the invention without *in vivo* working examples in appellant's specification, once he was able to obtain such labeled peptides. Furthermore, the targeting of antibodies and fragments for imaging is well known in the art.

Finally, the examiner's position with respect to enablement in this case is at odds with the position she took on this issue in the parent application, now issued as U.S. 6,358,489. In that case, the examiner had no concern with a method of labeling any thiol-containing peptide with F-18, even though the claim encompasses peptides of many structures. Since the examiner concedes that the making of antibodies to any immunogen is straightforward, and the present specification enables a skilled artisan to make many different F-18 radiolabeled peptides, then the present claims to methods of detecting tissue using these bispecific antibodies and fragments to the radiolabeled peptides necessarily must be enabled.

The specification also provides a written description of the invention that clearly apprises those of skill in the relevant art that appellant had possession of the claimed invention at the time of filing. Determination of whether possession of the subject matter of an original claim has been demonstrated is guided by the USPTO Written Description Guidelines, and appellant has demonstrated possession of the full scope of the genus defined in claim 9 in accordance with the Guidelines. The

Guidelines note that the level of skill in the antibody art is very high, and that it is well known that antibodies can be made against virtually any protein. Therefore, once possession of the genus of F-18 labeled peptides is demonstrated, possession of bispecific antibodies specific to these peptides necessarily must follow. The specification describes the genus of F-18 labeled peptides in great detail, and thus an adequate written description of all claims is contained within appellant's disclosure.

IX. ARGUMENT

A. The specification enables the detection of tissue using bispecific antibodies and fragments with one arm specific to a targeted tissue and one arm specific to an F-18 labeled peptide other than the labeled peptides specifically recited in claims 13-15.

i. The examiner's stated rejection

Claims 9-12 and 16-20 are rejected under the first paragraph of Section 112. The examiner alleges that the specification only is enabling for a method for detecting a tissue in a patient by administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to one of the specific F-18 labeled peptides that are recited in claims 13-15, or a low molecular weight hapten conjugated to one of these F-18 labeled peptides, and then administering one of the specific F-18 labeled peptides recited in claims 13-15 or the hapten conjugate thereof, and detecting that F-18 labeled peptide by positron emission tomography. The examiner finds that methods that use bispecific antibodies and antibody fragments in which the other arm is specific to "any F-18 labeled peptide or any low molecular weight hapten conjugated to any F-18 labeled peptide" are not enabled. In addition, the examiner more particularly finds the following methods not to be enabled:

1. those in which the F-18 labeled peptide contains a thiol group (claim 10 and 12);
2. those in which the F-18-labeled peptide is labeled by a method comprising reacting a peptide comprising a free thiol group with a labelling reagent having the general formula $^{18}\text{F}-(\text{CH}_2)_m-\text{CR}_1\text{R}_2-(\text{CH}_2)_n-\text{X}$ (claim 11);
3. those in which the hapten is any metal chelate complex (claim 16);
4. those in which metal chelate complex comprises manganese, iron or gadolinium (claim 17);
5. those in which the bispecific antibody or antibody fragment is *any* monoclonal or *any* humanized antibody (claim 19); and
6. those in which the F-18 labeled peptide is detected by positron emission tomography (claim 20).

ii. Neither the fact that the structure of an F-18 labeled peptide is not specified, nor the fact that different peptide sequences produce antibodies that have different specificities, leads to a conclusion of lack of enablement for bispecific antibodies and fragments that are specific to an F-18 labeled peptide.

The primary argument presented in support of lack of enablement is that, other than the specific F-18 labeled peptides recited in claims 13-15, there is insufficient guidance about the structure (amino acid residues) of any of the F-18 labeled peptides. The examiner elaborates that "without the specific amino acid residues, one of skill in the art cannot even contemplate of making such antibody that would have one arm specific for any F-18 labeled peptide and one arm would be specific for any tissue in a patient." She cites Kuby *et al.* as showing that "immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in

antibody specificity that differs from antibody specificity directed against the native full-length polypeptide."

Yet the making of antibodies to **any** immunogen is a straightforward and routine matter. More particularly, antibodies to peptide backbones are generated by well-known methods for antibody production. For example, injection of an immunogen, such as (peptide)_n-KLH, wherein KLH is keyhole limpet hemocyanin, and n = 1-30, in complete Freund's adjuvant, followed by two subsequent injections of the same immunogen suspended in incomplete Freund's adjuvant into immunocompetent animals, is followed three days after an i.v. boost of antigen, by spleen cell harvesting. Harvested spleen cells are then fused with Sp2/O-Ag14 myeloma cells and culture supernatants of the resulting clones analyzed for anti-peptide reactivity using a direct-binding ELISA. Fine specificity of generated antibodies can be analyzed for by using peptide fragments of the original immunogen. These fragments can be prepared readily using an automated peptide synthesizer. For antibody production, enzyme-deficient hybridomas are isolated to enable selection of fused cell lines. This technique also can be used to raise antibodies to one or more of the low molecular weight haptens, chelates comprising the linker, e.g., In(III)-DTPA chelates. Monoclonal mouse antibodies to an In(III)-di-DTPA are known (Barbet *et al.*, U.S. Pat. Nos. 5,256,395).

After the initial raising of antibodies to the immunogen, the antibodies can be sequenced and subsequently prepared by recombinant techniques. Humanization and chimerization of murine antibodies and antibody fragments are well known to those skilled in the art. For example, humanized monoclonal antibodies are produced by transferring mouse complementary determining regions from heavy and light variable chains of the mouse immunoglobulin into a human variable domain, and then, substituting human residues in the framework regions of the murine counterparts. The use of antibody components derived from humanized monoclonal antibodies obviates potential problems associated with the

immunogenicity of murine constant regions. General techniques for cloning murine immunoglobulin variable domains are described, for example, by the publication of Orlandi *et al.*, *Proc. Nat'l Acad. Sci. USA* 86: 3833 (1989). Techniques for producing humanized Mabs are described, for example, by Jones *et al.*, *Nature* 321: 522 (1986), Riechmann *et al.*, *Nature* 332: 323 (1988), Verhoeyen *et al.*, *Science* 239: 1534 (1988), Carter *et al.*, *Proc. Nat'l Acad. Sci. USA* 89: 4285 (1992), Sandhu, *Crit. Rev. Biotech.* 12: 437 (1992), and Singer *et al.*, *J. Immun.* 150: 2844 (1993).

Alternatively, fully human antibodies can be obtained from transgenic non-human animals. See, *e.g.*, Mendez *et al.*, *Nature Genetics*, 15: 146-156 (1997); U.S. Pat. No. 5,633,425. For example, human antibodies can be recovered from transgenic mice possessing human immunoglobulin loci. The mouse humoral immune system is humanized by inactivating the endogenous immunoglobulin genes and introducing human immunoglobulin loci. The human immunoglobulin loci are exceedingly complex and comprise a large number of discrete segments which together occupy almost 0.2% of the human genome. To ensure that transgenic mice are capable of producing adequate repertoires of antibodies, large portions of human heavy- and light-chain loci must be introduced into the mouse genome. This is accomplished in a stepwise process beginning with the formation of yeast artificial chromosomes (YACs) containing either human heavy- or light-chain immunoglobulin loci in germline configuration. All of the foregoing description can be found in U.S. Serial no. 09/823,746, the regular filing of provisional application no. 60/090,142, which is mentioned on page 4 of the application and incorporated by reference.

Thus, a skilled artisan readily can generate antibodies to any immunogen, and from those antibodies can prepare antibody fragments that are specific to the immunogen. These antibodies and fragments may be monoclonal, as in claim 18, or humanized, as in claim 19. The fact that different peptide sequences produce

antibodies that have different specificities does not lead to a lack of enablement of the present claims, since a skilled artisan could generate an antibody for any peptide, without even knowing the amino acid sequence of the peptide! As noted by the examiner, in addition to having different specificities, antibodies to different peptides also may have different affinities. However, the determination of affinities, and the selection of those antibodies with the best affinities, also are routine and within the level of skill in this art.

Following this explanation by appellant, the examiner admitted that "the method of making antibodies to any immunogen appears to be straightforward" (Official Action at page 5, lines 16-17). She urged, however, that "the term 'comprising' is open-ended. It expands the F-18 labeled peptide to include additional amino acid at either or both ends" is not understand. On the one hand, the examiner urges that the structure of the F-18 peptide is not known, while on the other she urges that the term "comprising" means that it may include additional amino acids at either end. The term "F-18 labeled peptide" in claim 9 covers, in the first instance, peptides with differing numbers of amino acid residues. It is therefore not understood how the term "comprising" could possibly "expand" the scope of the claimed peptide.

iii. Bispecific antibodies and fragments that have "an arm that is specific to a target tissue of the patient" also are fully enabled.

In the Advisory Action the examiner agreed that "the F-18 peptide may be used as immunogen to generate antibody that is specific for the F-18 peptide," but countered that "the binding specificity of the other half of the bispecific antibody is not disclosed, much less using the undisclosed bispecific for any purpose." Bispecific antibodies with "an arm specific for a target tissue," and their used in detection methods, were well known in this art as of the filing date. For example, U.S. Patent No. 4,925,648, filed July 29, 1998, discloses polyspecific anti-leukocyte antibody conjugate for targeting foci of leukocyte accretion comprises an

immunoreactive polyspecific composite of at least two different substantially monospecific antibodies or antibody fragments, conjugated to at least one imaging agent, wherein at least two of said antibodies or antibody fragments specifically bind to different leukocyte cell types. U.S. Patent No. 5,364,612, filed May 6, 1991, describes methods for detecting and imaging cardiovascular lesions such as atherosclerotic plaques, vascular clots including thrombi and emboli, myocardial infarction, and other organ infarcts, using multispecific antibody imaging agent conjugates specific for at least two different antigens selected from the group consisting of fibrin-, myosin- and platelet associated antigens. Therefore, the use of bispecific antibodies and fragments, having a binding specificity for "a target tissue" were well known in the art.

iv. The other bases for lack of enablement are similarly unfounded.

As noted above, six other bases for lack of enablement are urged by the examiner. These relate to methods in which:

1. the F-18 labeled contains a thiol group (claims 10 and 12);
2. the F-18-labeled peptide is labeled by a method comprising reacting a peptide comprising a free thiol group with a labeling reagent having the general formula $^{18}\text{F}-(\text{CH}_2)_m-\text{CR}_1\text{R}_2-(\text{CH}_2)_n-\text{X}$ (claim 11);
3. the hapten is any metal chelate complex (claim 16);
4. the metal chelate complex comprises manganese, iron or gadolinium (claim 17);
5. the bispecific antibody or antibody fragment is *any* monoclonal or *any* humanized antibody (claims 18 and 19); and

6. the F-18 labeled peptide is detected by positron emission tomography (claim 20).

It is well settled that such naked assertions of non-enablement cannot sustain a rejection under section 112. No additional reasons in support of five of the six assertions is provided. With respect to the sixth, the examiner argues that "there is [sic: are] no *vivo* [sic: *in vivo*] working examples demonstrating that any antibody with unknown specificity would be useful in a method of detecting a tissue in a patient using PET." As detailed in the background of appellant's specification, in the clinical setting, fluorine-18 (F-18) is one of the most widely used positron-emitting nuclides. It is its short half-life of F-18 that has limited or precluded its use with longer-lived specific targeting vectors such as antibodies, antibody fragments, recombinant antibody constructs and longer-lived receptor-targeted peptides. Prior to the present invention, complicated chemistry has been required to link the inorganic fluoride species to such organic targeting vectors. The present invention provides a simple, efficient method for incorporating the F-18 radionuclide into peptide-containing targeting vectors, such as proteins, antibodies, antibody fragments, and receptor-targeted peptides, to allow the use of such targeting vectors in routine clinical positron emission tomography. PET with F-18 in other embodiments is considered a routine clinical procedure. Furthermore, the targeting of antibodies and fragments for imaging is well known in the art. Therefore, a skilled clinician would be fully enabled to practice PET with bispecific antibodies and fragments with one specific to a target tissue and another arm specific to an F-18 labeled peptides according to the invention without *in vivo* working examples in appellant's specification.

v. The examiner's position with respect to enablement in this case is at odds with the position she took on this issue in the parent application, now issued as U.S. 6,358,489.

The examiner's position with respect to enablement in this case is directly at odds with the position she took on this issue in the parent application, now issued

as U.S. 6,358,489. Claim 1 of the issued patent recites "A method for radiolabeling thiol-containing peptide with fluorine-18 (F-18), comprising reacting a peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate and triflate." Thus, the examiner had no concern with a method of labeling *any* thiol-containing peptide with F-18, even though the claim encompasses peptides of many structures. Since the examiner concedes that the making of antibodies to any immunogen is straightforward, and the present specification enables a skilled artisan to make many different F-18 radiolabeled peptides, then the present claims to methods of detecting tissue using these antibodies to the radiolabeled peptides necessarily must be enabled.

B. The specification also provides a written description of the invention that clearly apprises those of skill in the relevant art that appellant had possession of the claimed invention at the time of filing.

- i. Determination of whether possession of the subject matter of an original claim has been demonstrated is guided by the USPTO Written Description Guidelines.

While a question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently, there is a strong presumption that an adequate written description of an original claim is present in the specification as filed.⁸ The examiner, however cites *The Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). In response to this case, the USPTO promulgated written description guidelines to help examiners determine whether claims are enabled. In particular, a decision tree is provided for consideration of original claims, as here.

⁸ MPEP §2163.03.

As to original claims, possession may be shown in many ways. For example, possession may be shown, *inter alia*, by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.⁹

For each claim drawn to a genus, as in claim 9, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice. A representative number of species means that the species which are adequately described are representative of the entire genus. There may be situations where one species adequately supports a genus. Furthermore, what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.¹⁰

The Written Description Guidelines provide an outline of factors to be considered in determining whether an original genus claim is enabled. The decision tree for original genus claims begins with a determination of whether the art indicates substantial variation among the species within the genus of the claimed

⁹ USPTO Written Description Guidelines.

¹⁰ USPTO Written Description Guidelines.

subject matter, followed by immediately by a determination of whether a representative number of species are implicitly or explicitly disclosed. The decision tree notes that what is a representative number of species depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed.

- ii. Appellant has demonstrated possession of the full scope of the genus defined in claims 9-12 and 16-20.

The species of claims 13-15 have been found by the examiner to be allowable, and only the genus claims are rejected. The genus defines bispecific antibodies and fragments in which one arm is specific to a targeted tissue and the other arm is specific to "an F-18-labeled peptide or a low molecular weight hapten conjugated to the F-18-labeled peptide." A consideration of the factors specific to this case leads inescapably to a conclusion that appellant had possession of the genus of bispecific antibodies and fragments with one arm specific to a targeted tissue and one arm specific to "an F-18 labeled peptide" that is recited in claim 9 at the time of filing.

An important factor in the consideration of whether appellant had possession of the genus claimed in claim 9 turns heavily on the level of skill in the relevant art. The level of skill in the antibody art is very high. Indeed, the portion of the Written Description Guidelines relating to antibody claims notes that:

The general knowledge in the art is such that antibodies are structurally well-characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgD, IgD, IgA and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antibody binding sites in the form of complementarity determining regions and the framework regions. The sequences of the common regions as well as the variable region subgroups (framework regions) from a variety of species are known

and published in the art. ***It is also well known that antibodies can be made against virtually any protein... This is a mature technology where the level of skill is high and advanced.***

Emphasis added.

Based on this, and the teaching found in the present disclosure, appellant has demonstrated possession of bispecific antibodies and fragments across the full scope of bispecific antibodies and fragments having separate arms specific for targeted tissues and F-18 labeled peptides. As noted above, antigens associated with targeted tissues, and bispecific antibodies and fragments specific to these antigens are well known in the art, and therefore the highly skilled artisans in this field are in possession of antibodies and fragments to targeted tissues.¹¹ Similarly, once possession of the genus of F-18 labeled peptides is demonstrated, possession of bispecific antibodies and fragments specific to these peptides necessarily must follow. The only issue, therefore, is whether the specification sufficiently describes the genus of F-18 labeled peptides. It does so in great detail, with a major portion of the disclosure being devoted to a description of what such peptides encompass and how they may be made.

The present invention provides simple and efficient methods for incorporating the F-18 radionuclide into peptide-containing targeting vectors, such as proteins, antibodies, antibody fragments and receptor-targeted peptides. The disclosure defines the term "peptide" as including proteins, antibodies, antibody fragments and receptor-targeted peptides. The methods of the present invention makes such targeting vectors available for routine clinical positron emission tomography.

Of all nucleophiles present on peptides, only a free thiol group can be rapidly alkylated at neutral pH and moderate temperature. The present invention takes advantage of this unique property of free thiol groups, and provides methods for labelling thiol-containing peptides with F-18.

The specification teaches a method for labeling any thiol-containing peptide and then making an antibody to that peptide. The technique for making the peptide entails reacting the thiol group with an F-18 bound labeling reagent which has a group that is reactive with thiols. Even peptides that do not originally comprise a free thiol group can be labeled in accordance with the present invention by first modifying the peptide to add a free thiol group by methods known to those skilled in the art. For example, the peptide can be thiolated with reagents such as 2-iminothiolane, or intrinsic disulfide bonds such as cysteine residues can be reduced. A combination of both modifications also can be performed, such as acylation of lysine residues with N-succinimidyl-3-(2-pyridylthio)-propionate (SPDP) followed by the controlled reduction of the appended disulfide bond. These techniques are discussed at the top of page 6. Thus, the specification evidences possession of the genus of F-18 labeled peptides across its full scope. Since the level of skill in this art is very high and "antibodies can be made against virtually any protein" appellant's possession of bispecific antibodies and fragments in which one arm is specific to an F-18 labeled peptide is manifest.

C. While no issue of enablement or written description exists with respect to any of the claims, there is a separate basis for patentability of each of claims 10, 11 and 12.

In *Eli Lilly*, the patent in suit contained generic claims to cDNA encoding mammalian insulin. The patent exemplified the cDNA for rat insulin, and gave a procedure for isolating the human insulin cDNA. The court found this disclosure insufficient to satisfy the written description requirement. The court stressed that the written description of an invention must be "sufficient to distinguish it from other materials." While the case related to cDNA, the court provided some guidance on claims involving chemical materials, stating that:

¹¹ Section IX.A.iii., *supra*, last paragraph.

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass.

119 F.3d at 1568.

Claim 11 defines a generic formula indicating with specificity a subgenus of F-18 labeled peptides. Based on the quoted portion of *Lilly*, an additional basis for written description exists as to claim 11. Moreover, detailed guidance is provided in the specification regarding how to prepare F-18 labeled peptides as recited in claim 11, and therefore an additional basis for enablement exists as to claim 11.

While claims 10 and 12 do not include a generic formula, they do define subgenera of the genus defined in claim 9. Claim 10 describes methods in which the F-18-labeled peptide contains a thiol group, and claim 12 defines methods in which the F-18-labeled peptide is labeled by reacting a peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate and triflate. Therefore, there is additional basis in support of both the written description and enablement of claims 10 and 12.

X. CONCLUSION

For these reasons, the Board is respectfully requested to reverse the examiner and remand this application for issuance.

Respectfully submitted,

Nov. 12, 2003

Date



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APPENDIX: APPEALED CLAIMS

9. A method for detecting a tissue comprising:

(a) administering to a patient a bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to an F-18-labeled peptide or a low molecular weight hapten conjugated to the F-18-labeled peptide; and allowing the bispecific antibody or antibody fragment to bind to the target tissue, and the non-targeted bispecific antibody or antibody fragment to clear;

(b) administering the F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing the F-18-labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear; and

(c) detecting the F-18-labeled peptide, thereby detecting the target tissue.

10. The method according to claim 9, wherein the F-18-labeled peptide contains a thiol group.

11. (Amended) The method according to claim 10, wherein the F-18-labeled peptide is labeled by a method comprising reacting a peptide comprising a free thiol group with a labelling reagent having the general formula $^{18}\text{F}-(\text{CH}_2)_m-\text{CR}_1\text{R}_2-(\text{CH}_2)_n-\text{X}$, wherein:

n is 0, 1 or 2;

m is 0, 1 or 2;

and n + m is 0, 1, or 2;

X is selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, unsubstituted maleimide, maleimide substituted with one or two alkyl groups, and 3-sulfo-maleimide; and

R₁ and R₂ are the same or different and are selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, hydrogen, -CONH₂, carboxyl, hydroxyl, sulfonic acid, tertiary amine, quaternary ammonium, unsubstituted alkyl, substituted alkyl, -COOR', -CONR'₂, or COR', wherein the substituents of the substituted alkyl groups are selected from the group consisting of -CONH₂, carboxyl, hydroxyl, sulfonic acid, tertiary amine and quaternary ammonium and wherein R' is a C₁-C₆ alkyl or phenyl.

12. (Amended) The method according to claim 10, wherein the F-18-labeled peptide is labeled by a method comprising reacting a peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate and triflate.

16. The method according to claim 9, wherein the hapten is a metal chelate complex.

17. The method according to claim 16, wherein the metal chelate complex comprises manganese, iron, or gadolinium.

18. The method according to claim 9, wherein the bispecific antibody or antibody fragment is monoclonal.

19. The method according to claim 9, wherein the antibody or antibody fragment is humanized.

20. The method according to claim 9, wherein the F-18-labeled peptide is detected by positron emission tomography.



Serial No. 10/071,247

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: Gary Griffiths

Title: FLUORINATION OF PROTEINS AND
PEPTIDES FOR F-18 POSITRON
EMISSION TOMOGRAPHY

Appl. No.: 10/071,247

Filing Date: 02/11/2002

Examiner: Huynh, P.

Art Unit: 1644

BRIEF ON APPEAL



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Attorney Docket No. 018733/1093

Applicant: Gary Griffiths

Title: FLUORINATION OF PROTEINS AND
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Appl. No.: 10/071,247

Filing Date: 02/11/2002

Examiner: Huynh, P.

Art Unit: 1644

APPELLANT'S BRIEF UNDER 37 CFR §1.192

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

This brief is in furtherance of the Notice of Appeal filed in this case on September 11, 2003. The fees required under 37 CFR §1.17(f) are included in the attached check. Please charge any fee deficiency or credit any overpayment to Deposit Account 19-0741.

This brief is transmitted in triplicate in conformance with 37 CFR §1.192(a).

I. REAL PARTY IN INTEREST

The real party in interest in this case is Immunomedics, Inc., as evidenced by an assignment recorded on February 4, 1999 at Reel/Frame 9759/0057.

II. RELATED APPEALS AND INTERFERENCES

Appellant, appellant's legal representatives, and the assignee are aware of no appeal or interference which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Canceled: 1-8

Pending: 9-20

Objected: 13-15

Rejected: 9-12 and 16-20

Appealed: 9-12 and 16-20

IV. STATUS OF AMENDMENTS

All claim amendments have been entered into the record, and appellant's arguments after Final Rejection have been considered, as indicated in an Advisory Action dated September 8, 2003.

V. BACKGROUND AND SUMMARY OF THE INVENTION

Positron emission tomography (PET) is a high resolution, non-invasive, imaging technique for the visualization of human disease. In PET, 511 keV gamma photons produced during positron annihilation decay are detected. In the clinical setting, fluorine-18 (F-18) is one of the most widely used positron-emitting nuclides. F-18 has a half-life ($t_{1/2}$) of 110 minutes, and emits β^+ particles at an energy of 635 keV. It is 97% abundant.¹

¹ Specification at page 1, lines 13-18.

The short half-life of F-18 has limited or precluded its use with longer-lived specific targeting vectors such as antibodies, antibody fragments, recombinant antibody constructs and longer-lived receptor-targeted peptides. In addition, complicated chemistry has been required to link the inorganic fluoride species to such organic targeting vectors. In typical synthesis methods, an intermediate is radiofluorinated, and the F-18-labeled intermediate is purified for coupling to protein amino groups. See, e.g., Lang *et al.*, *Appl. Radiat. Isot.*, 45 (12): 1155-63 (1994); Vaidyanathan *et al.*, *Bioconj. Chem.*, 5: 352-56 (1994).²

These methods are tedious to perform and require the efforts of specialized professional chemists. They are not amenable to kit formulations for use in a clinical setting. Multiple purifications of intermediates are commonly required, and the final step, involving linkage to protein lysine residues, usually results in 30-60 % yields, necessitating a further purification step prior to patient administration. In addition, these methods result in fluorinated targeting species which accumulate in the kidney, somewhat like radiometals.³

It was recently reported that ^{18}F -fluoroiodomethane ($^{18}\text{FCH}_2\text{I}$) is a useful intermediate for the fluorination of organic intermediates. Zheng *et al.*, *J. Nucl. Med.*, 38: 177P (Abs. 761) (1997). In this process, diiodomethane is fluorinated with the F-18 ion by a room temperature reaction in acetonitrile solvent, resulting in up to a 40% yield. The $^{18}\text{FCH}_2\text{I}$ is then distilled into reaction vials containing various strong nucleophiles in anhydrous acetonitrile and allowed to react at 80°C for fifteen minutes. Nucleophilic attack by carboxylates, thiolates, phenolates, and amines in particular, replaces the remaining iodine of $^{18}\text{FCH}_2\text{I}$, with overall yields of 10 to 35 %. The reaction products can be purified by reverse-phase HPLC. Fluoromethyl

² Specification at page 1, lines 19-26.

³ Specification at page 2, lines 1-7.

diethylamine, fluoromethyl benzoate, fluoromethyl benzyl thioether and fluoromethyl 4-(2-hydroxy-3-aminopropoxy)-carbazole have been made by this method.⁴

As discussed above, the currently available methods for labeling protein-based targeting vectors with F-18 are unsuitable. There is a need, therefore, for a simple, efficient method for incorporating the F-18 radionuclide into peptide-containing targeting vectors, such as proteins, antibodies, antibody fragments, and receptor-targeted peptides, to allow the use of such targeting vectors in routine clinical positron emission tomography.⁵

The present invention teaches methods for radiolabeling proteins and peptides with fluorine-18 (F-18). More particularly, these proteins and peptides are radiolabeled with F-18 by reacting a thiol group contained therein with an F-18-bound labeling reagent which also has a group that is reactive with thiols. The resulting F-18-labeled proteins and peptides are useful in imaging targeted tissue by clinical positron emission tomography.⁶

More particularly, the claims on appeal are directed to methods for detecting a tissue, comprising:

(a) administering to a patient a bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to an F-18-labeled peptide or a low molecular weight hapten conjugated to the F-18-labeled peptide; and allowing the bispecific antibody or antibody fragment to bind to the target tissue, and the non-targeted bispecific antibody or antibody fragment to clear;

⁴ Specification at page 2, lines 8-18.

⁵ Specification at page 2, lines 19-24.

⁶ Specification at page 1, lines 6-11.

(b) administering the F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing the F-18-labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear; and

(c) detecting the F-18-labeled peptide, thereby detecting the target tissue.⁷

VI. ISSUES

There are two issues in the present case, both stated under the first paragraph of Section 112.

The first issue is whether the specification enables a skilled artisan to practice the invention as recited in claims 9-12 and 16-20.

The second issue is whether the specification reasonably provides a written description of the invention, such that those skilled in the relevant art are apprised that the inventor, at the time the application was filed, had possession of the invention claimed in claims -12 and 16-20.

VII. GROUPS OF CLAIMS

For purposes of the present appeal, the claims do not all stand or fall together, but will be argued separately according to the following groups:

Group 1 Claims 9 and 16-20

Group 2 Claim 11

Group 3 Claims 10 and 12

⁷ See claim 9.

Arguments supporting patentability of Group 1 are found in Section IX.A. and IX.B. of the Brief. Arguments demonstrating additional bases for patentability of Groups 2 and 3, respectively, are presented in Section IX.C. of the Brief.

VIII. SUMMARY OF THE ARGUMENT

In general, the rejections appear to be based on a misunderstanding. The presently claimed invention is utilized in a wide range of known bi-specific antibodies and provides the chemistry to successfully label F-18 onto a wide variety of peptides for use in these known methods. The rejections improperly focus on the unpredictability of amino acid sequences rather than on the question of whether one of ordinary skill could successfully apply the labeling technique to diverse amino acid sequences. As to this latter issue, nothing in the rejections suggests only such difficulties. The specification enables the detection of tissue using bispecific antibodies and fragments having one arm specific to F-18 labeled peptides other than those specifically recited in claims 13-15. Although the examiner alleges that the specification only is enabling for a method for detecting a tissue in a patient by administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to one of the specific F-18 labeled peptides that are recited in claims 13-15, or a low molecular weight hapten conjugated to one of these F-18 labeled peptides, and then administering one of the specific F-18 labeled peptides recited in claims 13-15 or the hapten conjugate thereof, and detecting that F-18 labeled peptide by positron emission tomography, the record indicates that a skilled artisan is able to practice the invention across the full scope of claim 9. Neither the fact that the structure of an F-18 labeled peptide is not specified, nor the fact that different peptide sequences produce antibodies that have different specificities, leads to a conclusion of lack of enablement for bispecific antibodies and fragments that are specific to an F-18 labeled peptide. Similarly, bispecific

antibodies and fragments that have “an arm that is specific to a target tissue of the patient” also are fully enabled.

The other bases for lack of enablement are similarly unfounded. No additional reasons in support of five of six listed embodiments is provided. With respect to the last, the examiner argues that there are no *in vivo* working examples demonstrating that any antibody with unknown specificity would be useful in a method of detecting a tissue in a patient using PET. However, in the clinical setting, fluorine-18 (F-18) is one of the most widely used positron-emitting nuclides, and a skilled clinician would be fully enabled to practice PET with the F-18 labeled peptides according to the invention without *in vivo* working examples in appellant’s specification, once he was able to obtain such labeled peptides. Furthermore, the targeting of antibodies and fragments for imaging is well known in the art.

Finally, the examiner’s position with respect to enablement in this case is at odds with the position she took on this issue in the parent application, now issued as U.S. 6,358,489. In that case, the examiner had no concern with a method of labeling any thiol-containing peptide with F-18, even though the claim encompasses peptides of many structures. Since the examiner concedes that the making of antibodies to any immunogen is straightforward, and the present specification enables a skilled artisan to make many different F-18 radiolabeled peptides, then the present claims to methods of detecting tissue using these bispecific antibodies and fragments to the radiolabeled peptides necessarily must be enabled.

The specification also provides a written description of the invention that clearly apprises those of skill in the relevant art that appellant had possession of the claimed invention at the time of filing. Determination of whether possession of the subject matter of an original claim has been demonstrated is guided by the USPTO Written Description Guidelines, and appellant has demonstrated possession of the full scope of the genus defined in claim 9 in accordance with the Guidelines. The

Guidelines note that the level of skill in the antibody art is very high, and that it is well known that antibodies can be made against virtually any protein. Therefore, once possession of the genus of F-18 labeled peptides is demonstrated, possession of bispecific antibodies specific to these peptides necessarily must follow. The specification describes the genus of F-18 labeled peptides in great detail, and thus an adequate written description of all claims is contained within appellant's disclosure.

IX. ARGUMENT

A. The specification enables the detection of tissue using bispecific antibodies and fragments with one arm specific to a targeted tissue and one arm specific to an F-18 labeled peptide other than the labeled peptides specifically recited in claims 13-15.

i. The examiner's stated rejection

Claims 9-12 and 16-20 are rejected under the first paragraph of Section 112. The examiner alleges that the specification only is enabling for a method for detecting a tissue in a patient by administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to one of the specific F-18 labeled peptides that are recited in claims 13-15, or a low molecular weight hapten conjugated to one of these F-18 labeled peptides, and then administering one of the specific F-18 labeled peptides recited in claims 13-15 or the hapten conjugate thereof, and detecting that F-18 labeled peptide by positron emission tomography. The examiner finds that methods that use bispecific antibodies and antibody fragments in which the other arm is specific to "any F-18 labeled peptide or any low molecular weight hapten conjugated to any F-18 labeled peptide" are not enabled. In addition, the examiner more particularly finds the following methods not to be enabled:

1. those in which the F-18 labeled peptide contains a thiol group (claim 10 and 12);
2. those in which the F-18-labeled peptide is labeled by a method comprising reacting a peptide comprising a free thiol group with a labelling reagent having the general formula $^{18}\text{F}-(\text{CH}_2)_m-\text{CR}_1\text{R}_2-(\text{CH}_2)_n-\text{X}$ (claim 11);
3. those in which the hapten is any metal chelate complex (claim 16);
4. those in which metal chelate complex comprises manganese, iron or gadolinium (claim 17);
5. those in which the bispecific antibody or antibody fragment is *any* monoclonal or *any* humanized antibody (claim 19); and
6. those in which the F-18 labeled peptide is detected by positron emission tomography (claim 20).

ii. Neither the fact that the structure of an F-18 labeled peptide is not specified, nor the fact that different peptide sequences produce antibodies that have different specificities, leads to a conclusion of lack of enablement for bispecific antibodies and fragments that are specific to an F-18 labeled peptide.

The primary argument presented in support of lack of enablement is that, other than the specific F-18 labeled peptides recited in claims 13-15, there is insufficient guidance about the structure (amino acid residues) of any of the F-18 labeled peptides. The examiner elaborates that "without the specific amino acid residues, one of skill in the art cannot even contemplate of making such antibody that would have one arm specific for any F-18 labeled peptide and one arm would be specific for any tissue in a patient." She cites Kuby *et al.* as showing that "immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in

antibody specificity that differs from antibody specificity directed against the native full-length polypeptide.”

Yet the making of antibodies to *any* immunogen is a straightforward and routine matter. More particularly, antibodies to peptide backbones are generated by well-known methods for antibody production. For example, injection of an immunogen, such as (peptide)_n-KLH, wherein KLH is keyhole limpet hemocyanin, and n = 1-30, in complete Freund's adjuvant, followed by two subsequent injections of the same immunogen suspended in incomplete Freund's adjuvant into immunocompetent animals, is followed three days after an i.v. boost of antigen, by spleen cell harvesting. Harvested spleen cells are then fused with Sp2/O-Ag14 myeloma cells and culture supernatants of the resulting clones analyzed for anti-peptide reactivity using a direct-binding ELISA. Fine specificity of generated antibodies can be analyzed for by using peptide fragments of the original immunogen. These fragments can be prepared readily using an automated peptide synthesizer. For antibody production, enzyme-deficient hybridomas are isolated to enable selection of fused cell lines. This technique also can be used to raise antibodies to one or more of the low molecular weight haptens, chelates comprising the linker, e.g., In(III)-DTPA chelates. Monoclonal mouse antibodies to an In(III)-di-DTPA are known (Barbet *et al.*, U.S. Pat. Nos. 5,256,395).

After the initial raising of antibodies to the immunogen, the antibodies can be sequenced and subsequently prepared by recombinant techniques. Humanization and chimerization of murine antibodies and antibody fragments are well known to those skilled in the art. For example, humanized monoclonal antibodies are produced by transferring mouse complementary determining regions from heavy and light variable chains of the mouse immunoglobulin into a human variable domain, and then, substituting human residues in the framework regions of the murine counterparts. The use of antibody components derived from humanized monoclonal antibodies obviates potential problems associated with the

immunogenicity of murine constant regions. General techniques for cloning murine immunoglobulin variable domains are described, for example, by the publication of Orlandi *et al.*, *Proc. Nat'l Acad. Sci. USA* 86: 3833 (1989). Techniques for producing humanized Mabs are described, for example, by Jones *et al.*, *Nature* 321: 522 (1986), Riechmann *et al.*, *Nature* 332: 323 (1988), Verhoeyen *et al.*, *Science* 239: 1534 (1988), Carter *et al.*, *Proc. Nat'l Acad. Sci. USA* 89: 4285 (1992), Sandhu, *Crit. Rev. Biotech.* 12: 437 (1992), and Singer *et al.*, *J. Immun.* 150: 2844 (1993).

Alternatively, fully human antibodies can be obtained from transgenic non-human animals. See, *e.g.*, Mendez *et al.*, *Nature Genetics*, 15: 146-156 (1997); U.S. Pat. No. 5,633,425. For example, human antibodies can be recovered from transgenic mice possessing human immunoglobulin loci. The mouse humoral immune system is humanized by inactivating the endogenous immunoglobulin genes and introducing human immunoglobulin loci. The human immunoglobulin loci are exceedingly complex and comprise a large number of discrete segments which together occupy almost 0.2% of the human genome. To ensure that transgenic mice are capable of producing adequate repertoires of antibodies, large portions of human heavy- and light-chain loci must be introduced into the mouse genome. This is accomplished in a stepwise process beginning with the formation of yeast artificial chromosomes (YACs) containing either human heavy- or light-chain immunoglobulin loci in germline configuration. All of the foregoing description can be found in U.S. Serial no. 09/823,746, the regular filing of provisional application no. 60/090,142, which is mentioned on page 4 of the application and incorporated by reference.

Thus, a skilled artisan readily can generate antibodies to any immunogen, and from those antibodies can prepare antibody fragments that are specific to the immunogen. These antibodies and fragments may be monoclonal, as in claim 18, or humanized, as in claim 19. The fact that different peptide sequences produce

antibodies that have different specificities does not lead to a lack of enablement of the present claims, since a skilled artisan could generate an antibody for any peptide, without even knowing the amino acid sequence of the peptide! As noted by the examiner, in addition to having different specificities, antibodies to different peptides also may have different affinities. However, the determination of affinities, and the selection of those antibodies with the best affinities, also are routine and within the level of skill in this art.

Following this explanation by appellant, the examiner admitted that "the method of making antibodies to any immunogen appears to be straightforward" (Official Action at page 5, lines 16-17). She urged, however, that "the term 'comprising' is open-ended. It expands the F-18 labeled peptide to include additional amino acid at either or both ends" is not understood. On the one hand, the examiner urges that the structure of the F-18 peptide is not known, while on the other she urges that the term "comprising" means that it may include additional amino acids at either end. The term "F-18 labeled peptide" in claim 9 covers, in the first instance, peptides with differing numbers of amino acid residues. It is therefore not understood how the term "comprising" could possibly "expand" the scope of the claimed peptide.

iii. Bispecific antibodies and fragments that have "an arm that is specific to a target tissue of the patient" also are fully enabled.

In the Advisory Action the examiner agreed that "the F-18 peptide may be used as immunogen to generate antibody that is specific for the F-18 peptide," but countered that "the binding specificity of the other half of the bispecific antibody is not disclosed, much less using the undisclosed bispecific for any purpose." Bispecific antibodies with "an arm specific for a target tissue," and their use in detection methods, were well known in this art as of the filing date. For example, U.S. Patent No. 4,925,648, filed July 29, 1998, discloses polyspecific anti-leukocyte antibody conjugate for targeting foci of leukocyte accretion comprises an

immunoreactive polyspecific composite of at least two different substantially monospecific antibodies or antibody fragments, conjugated to at least one imaging agent, wherein at least two of said antibodies or antibody fragments specifically bind to different leukocyte cell types. U.S. Patent No. 5,364,612, filed May 6, 1991, describes methods for detecting and imaging cardiovascular lesions such as atherosclerotic plaques, vascular clots including thrombi and emboli, myocardial infarction, and other organ infarcts, using multispecific antibody imaging agent conjugates specific for at least two different antigens selected from the group consisting of fibrin-, myosin- and platelet associated antigens. Therefore, the use of bispecific antibodies and fragments, having a binding specificity for "a target tissue" were well known in the art.

iv. The other bases for lack of enablement are similarly unfounded.

As noted above, six other bases for lack of enablement are urged by the examiner. These relate to methods in which:

1. the F-18 labeled contains a thiol group (claims 10 and 12);
2. the F-18-labeled peptide is labeled by a method comprising reacting a peptide comprising a free thiol group with a labeling reagent having the general formula $^{18}\text{F}-(\text{CH}_2)_m-\text{CR}_1\text{R}_2-(\text{CH}_2)_n-\text{X}$ (claim 11);
3. the hapten is any metal chelate complex (claim 16);
4. the metal chelate complex comprises manganese, iron or gadolinium (claim 17);
5. the bispecific antibody or antibody fragment is *any* monoclonal or *any* humanized antibody (claims 18 and 19); and

6. the F-18 labeled peptide is detected by positron emission tomography (claim 20).

It is well settled that such naked assertions of non-enablement cannot sustain a rejection under section 112. No additional reasons in support of five of the six assertions is provided. With respect to the sixth, the examiner argues that "there is [sic: are] no *vivo* [sic: *in vivo*] working examples demonstrating that any antibody with unknown specificity would be useful in a method of detecting a tissue in a patient using PET." As detailed in the background of appellant's specification, in the clinical setting, fluorine-18 (F-18) is one of the most widely used positron-emitting nuclides. It is its short half-life of F-18 that has limited or precluded its use with longer-lived specific targeting vectors such as antibodies, antibody fragments, recombinant antibody constructs and longer-lived receptor-targeted peptides. Prior to the present invention, complicated chemistry has been required to link the inorganic fluoride species to such organic targeting vectors. The present invention provides a simple, efficient method for incorporating the F-18 radionuclide into peptide-containing targeting vectors, such as proteins, antibodies, antibody fragments, and receptor-targeted peptides, to allow the use of such targeting vectors in routine clinical positron emission tomography. PET with F-18 in other embodiments is considered a routine clinical procedure. Furthermore, the targeting of antibodies and fragments for imaging is well known in the art. Therefore, a skilled clinician would be fully enabled to practice PET with bispecific antibodies and fragments with one specific to a target tissue and another arm specific to an F-18 labeled peptides according to the invention without *in vivo* working examples in appellant's specification.

v. The examiner's position with respect to enablement in this case is at odds with the position she took on this issue in the parent application, now issued as U.S. 6,358,489.

The examiner's position with respect to enablement in this case is directly at odds with the position she took on this issue in the parent application, now issued

as U.S. 6,358,489. Claim 1 of the issued patent recites "A method for radiolabeling thiol-containing peptide with fluorine-18 (F-18), comprising reacting a peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate and triflate." Thus, the examiner had no concern with a method of labeling *any* thiol-containing peptide with F-18, even though the claim encompasses peptides of many structures. Since the examiner concedes that the making of antibodies to any immunogen is straightforward, and the present specification enables a skilled artisan to make many different F-18 radiolabeled peptides, then the present claims to methods of detecting tissue using these antibodies to the radiolabeled peptides necessarily must be enabled.

B. The specification also provides a written description of the invention that clearly apprises those of skill in the relevant art that appellant had possession of the claimed invention at the time of filing.

- i. Determination of whether possession of the subject matter of an original claim has been demonstrated is guided by the USPTO Written Description Guidelines.

While a question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently, there is a strong presumption that an adequate written description of an original claim is present in the specification as filed.⁸ The examiner, however cites *The Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). In response to this case, the USPTO promulgated written description guidelines to help examiners determine whether claims are enabled. In particular, a decision tree is provided for consideration of original claims, as here.

⁸ MPEP §2163.03.

As to original claims, possession may be shown in many ways. For example, possession may be shown, *inter alia*, by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.⁹

For each claim drawn to a genus, as in claim 9, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice. A representative number of species means that the species which are adequately described are representative of the entire genus. There may be situations where one species adequately supports a genus. Furthermore, what constitutes a “representative number” is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a “representative number” depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.¹⁰

The Written Description Guidelines provide an outline of factors to be considered in determining whether an original genus claim is enabled. The decision tree for original genus claims begins with a determination of whether the art indicates substantial variation among the species within the genus of the claimed

⁹ USPTO Written Description Guidelines.

¹⁰ USPTO Written Description Guidelines.

subject matter, followed by immediately by a determination of whether a representative number of species are implicitly or explicitly disclosed. The decision tree notes that what is a representative number of species depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed.

- ii. Appellant has demonstrated possession of the full scope of the genus defined in claims 9-12 and 16-20.

The species of claims 13-15 have been found by the examiner to be allowable, and only the genus claims are rejected. The genus defines bispecific antibodies and fragments in which one arm is specific to a targeted tissue and the other arm is specific to "an F-18-labeled peptide or a low molecular weight hapten conjugated to the F-18-labeled peptide." A consideration of the factors specific to this case leads inescapably to a conclusion that appellant had possession of the genus of bispecific antibodies and fragments with one arm specific to a targeted tissue and one arm specific to "an F-18 labeled peptide" that is recited in claim 9 at the time of filing.

An important factor in the consideration of whether appellant had possession of the genus claimed in claim 9 turns heavily on the level of skill in the relevant art. The level of skill in the antibody art is very high. Indeed, the portion of the Written Description Guidelines relating to antibody claims notes that:

The general knowledge in the art is such that antibodies are structurally well-characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgD, IgD, IgA and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antibody binding sites in the form of complementarity determining regions and the framework regions. The sequences of the common regions as well as the variable region subgroups (framework regions) from a variety of species are known

and published in the art. ***It is also well known that antibodies can be made against virtually any protein... This is a mature technology where the level of skill is high and advanced.***

Emphasis added.

Based on this, and the teaching found in the present disclosure, appellant has demonstrated possession of bispecific antibodies and fragments across the full scope of bispecific antibodies and fragments having separate arms specific for targeted tissues and F-18 labeled peptides. As noted above, antigens associated with targeted tissues, and bispecific antibodies and fragments specific to these antigens are well known in the art, and therefore the highly skilled artisans in this field are in possession of antibodies and fragments to targeted tissues.¹¹ Similarly, once possession of the genus of F-18 labeled peptides is demonstrated, possession of bispecific antibodies and fragments specific to these peptides necessarily must follow. The only issue, therefore, is whether the specification sufficiently describes the genus of F-18 labeled peptides. It does so in great detail, with a major portion of the disclosure being devoted to a description of what such peptides encompass and how they may be made.

The present invention provides simple and efficient methods for incorporating the F-18 radionuclide into peptide-containing targeting vectors, such as proteins, antibodies, antibody fragments and receptor-targeted peptides. The disclosure defines the term "peptide" as including proteins, antibodies, antibody fragments and receptor-targeted peptides. The methods of the present invention makes such targeting vectors available for routine clinical positron emission tomography.

Of all nucleophiles present on peptides, only a free thiol group can be rapidly alkylated at neutral pH and moderate temperature. The present invention takes advantage of this unique property of free thiol groups, and provides methods for labelling thiol-containing peptides with F-18.

The specification teaches a method for labeling any thiol-containing peptide and then making an antibody to that peptide. The technique for making the peptide entails reacting the thiol group with an F-18 bound labeling reagent which has a group that is reactive with thiols. Even peptides that do not originally comprise a free thiol group can be labeled in accordance with the present invention by first modifying the peptide to add a free thiol group by methods known to those skilled in the art. For example, the peptide can be thiolated with reagents such as 2-iminothiolane, or intrinsic disulfide bonds such as cysteine residues can be reduced. A combination of both modifications also can be performed, such as acylation of lysine residues with N-succinimidyl-3-(2-pyridylthio)-propionate (SPDP) followed by the controlled reduction of the appended disulfide bond. These techniques are discussed at the top of page 6. Thus, the specification evidences possession of the genus of F-18 labeled peptides across its full scope. Since the level of skill in this art is very high and “antibodies can be made against virtually any protein” appellant’s possession of bispecific antibodies and fragments in which one arm is specific to an F-18 labeled peptide is manifest.

C. While no issue of enablement or written description exists with respect to any of the claims, there is a separate basis for patentability of each of claims 10, 11 and 12.

In *Eli Lilly*, the patent in suit contained generic claims to cDNA encoding mammalian insulin. The patent exemplified the cDNA for rat insulin, and gave a procedure for isolating the human insulin cDNA. The court found this disclosure insufficient to satisfy the written description requirement. The court stressed that the written description of an invention must be “sufficient to distinguish it from other materials.” While the case related to cDNA, the court provided some guidance on claims involving chemical materials, stating that:

¹¹ Section IX.A.iii., *supra*, last paragraph.

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass.

119 F.3d at 1568.

Claim 11 defines a generic formula indicating with specificity a subgenus of F-18 labeled peptides. Based on the quoted portion of *Lilly*, an additional basis for written description exists as to claim 11. Moreover, detailed guidance is provided in the specification regarding how to prepare F-18 labeled peptides as recited in claim 11, and therefore an additional basis for enablement exists as to claim 11.

While claims 10 and 12 do not include a generic formula, they do define subgenera of the genus define in claim 9. Claim 10 describes methods in which the F-18-labeled peptide contains a thiol group, and claim 12 defines methods in which the the F-18-labeled peptide is labeled by reacting a peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate and triflate. Therefore, there is additional basis in support of both the written description and enablement of claims 10 and 12.

X. CONCLUSION

For these reasons, the Board is respectfully requested to reverse the examiner and remand this application for issuance.

Respectfully submitted,

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APPENDIX: APPEALED CLAIMS

9. A method for detecting a tissue comprising:

(a) administering to a patient a bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to an F-18-labeled peptide or a low molecular weight hapten conjugated to the F-18-labeled peptide; and allowing the bispecific antibody or antibody fragment to bind to the target tissue, and the non-targeted bispecific antibody or antibody fragment to clear;

(b) administering the F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing the F-18-labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear; and

(c) detecting the F-18-labeled peptide, thereby detecting the target tissue.

10. The method according to claim 9, wherein the F-18-labeled peptide contains a thiol group.

11. (Amended) The method according to claim 10, wherein the F-18-labeled peptide is labeled by a method comprising reacting a peptide comprising a free thiol group with a labelling reagent having the general formula $^{18}\text{F}-(\text{CH}_2)_m-\text{CR}_1\text{R}_2-(\text{CH}_2)_n-\text{X}$, wherein:

n is 0, 1 or 2;

m is 0, 1 or 2;

and $n + m$ is 0, 1, or 2;

X is selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, unsubstituted maleimide, maleimide substituted with one or two alkyl groups, and 3-sulfo-maleimide; and

R₁ and R₂ are the same or different and are selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, hydrogen, -CONH₂, carboxyl, hydroxyl, sulfonic acid, tertiary amine, quaternary ammonium, unsubstituted alkyl, substituted alkyl, -COOR', -CONR'₂, or COR', wherein the substituents of the substituted alkyl groups are selected from the group consisting of -CONH₂, carboxyl, hydroxyl, sulfonic acid, tertiary amine and quaternary ammonium and wherein R' is a C₁-C₆ alkyl or phenyl.

12. (Amended) The method according to claim 10, wherein the F-18-labeled peptide is labeled by a method comprising reacting a peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate and triflate.

16. The method according to claim 9, wherein the hapten is a metal chelate complex.

17. The method according to claim 16, wherein the metal chelate complex comprises manganese, iron, or gadolinium.

18. The method according to claim 9, wherein the bispecific antibody or antibody fragment is monoclonal.

19. The method according to claim 9, wherein the antibody or antibody fragment is humanized.

20. The method according to claim 9, wherein the F-18-labeled peptide is detected by positron emission tomography.